SODIUM AND POTASSIUM AS NUTRITIONAL FACTORS IN THE GENESIS, TREATMENT AND PREVENTION OF HYPERTENSION

FRANCIS J. HADDY, M.D., PH.D.
Department of Physiology
Uniformed Services University of the Health Sciences
Bethesda, Maryland

THERE is evidence from both animals and man both for and against a role for dietary sodium in the genesis, treatment and prevention of hypertension.[1]

EVIDENCE FROM ANIMALS

In animals, excessive dietary sodium can increase arterial blood pressure, particularly when renal excretory function is impaired. For example, a proportion of normal rats slowly become hypertensive when fed a high salt diet. The rat can be made more sensitive to the salt by first surgically reducing renal mass; blood pressure now rises more regularly, more rapidly and to higher levels. The reverse is also the case. Impairment of ability to excrete sodium (by reducing renal mass, removing one kidney and wrapping the other, removing one kidney and constricting the renal artery to the other, or administering mineralocorticoids) can increase arterial blood pressure, particularly when sodium intake is increased. For example, in rats, 70% surgical reduction in renal mass produces hypertension on a normal salt diet and increasing dietary salt intake intensifies the hypertension. Recent studies suggest that these low renin models of hypertension have an agent in plasma, perhaps derived from the hypothalamus, that inhibits sodium-potassium pump activity in their arteries and hearts.[2]

Inbred strains of rats have been developed which regularly and rapidly become severely hypertensive when fed high salt diets, without the need for deliberate renal damage. When the kidneys of these salt-sensitive rats are transplanted to others resistant to salt and naturally normotensive, arterial blood pressure rises. The reverse procedure results in normal pressures in rats otherwise destined to become hypertensive when given a high salt diet. The potential for salt-induced hypertension in these genetically salt sensi-

tive rats seems therefore to reside in part in the kidney. Other studies suggest that the genetic defect in the kidney is inability to excrete salt normally. The potential for hypertension also seems to reside, in part, in the blood vessels; genetic models of hypertension have vascular smooth muscle cells with increased permeability to sodium. We speculate that the same abnormality in the luminal aspect of renal tubular cells causing hyperreabsorption of sodium is basic to the renal defect. Humoral transmission of hypertension, through parabiotic connection, from salt-sensitive to salt-resistant rats has also been demonstrated.

EVIDENCE FROM MAN

In man, decreased capacity of the kidney to excrete sodium, due to loss of renal tissue or to mineralocorticoid excess (endogenous or exogenous), is often associated with hypertension. Sodium restriction ameliorates and sodium administration exacerbates the hypertension. A low salt diet is effective for the hypertension of renal failure. There can be no doubt of the importance of salt and water retention in the genesis of this type of hypertension.

Its role in essential hypertension is not so clear. Diuretics which promote natriuresis lower arterial pressure in patients with essential hypertension, an effect that has made them a mainstay of antihypertensive therapy. Certain categories of patients respond better than others, suggesting that salt and water are more important in some patients than in others. For example, hypertensive patients with low plasma renin activity respond to diuretics with a significantly greater effect than hypertensive patients with normal plasma renin activity. A larger percentage of hypertensive black subjects respond to diuretics than of hypertensive white subjects, perhaps because they are prone to the low renin variety.

As in animals, recent studies suggest that patients with essential hypertension, particularly of the low renin variety, have a circulating sodium pump inhibitor and decreased sodium pump activity in their leukocytes. Patients with heritable essential hypertension also have evidence for abnormal sodium transport, independent of the sodium pump, in their red blood cells, i.e., reports suggest that their red cells are more permeable to sodium. The consequences of superimposing the sodium pump inhibitor on this increased permeability needs to be studied because it seems possible that such superimposition occurs when a patient with heritable essential hypertension ingests excessive salt. In particular, would superimposition of the inhibitor on increased permeability cause a further increase in intracellular sodium concentration and contractile activity in vascular smooth muscle?

Severe reduction in the salt intake (less than 1 g/day) sometimes ameliorates essential hypertension whereas increase in salt intake often aggravates it. About half of patients with essential hypertension respond to a 0.2 g/day sodium chloride diet with a 20 mm Hg decrease in blood pressure. However, whether salt restriction of lesser degrees reduces arterial pressure in patients with essential hypertension remains controversial. It does seem to reduce the amount of medication needed to keep blood pressure under control.

Epidemiologic surveys demonstrate more hypertension in acculturated societies which ingest much salt than in unacculturated societies which ingest little salt. For example, certain areas in Finland and Japan where salt intake is very high have a higher incidence of hypertension than certain primitive areas in the Solomon Islands where salt intake is very low, and where blood pressure also does not rise with age. On the other hand, sodium intake, as judged by 24-hour urinary excretion, is not clearly related to arterial pressure in adult communities, e.g., it is difficult to demonstrate a relationship between salt intake and blood pressure within the United States. This might be expected if most of the individuals in the community had a high salt intake, as is the case in the United States, and if the pathophysiological problem was an inability to excrete it in only a minority of them.

Feeding large amounts of salt for short periods of time to normal human volunteers has only small effects on blood pressure. Feeding moderate amounts for long periods of time to normal human subjects has not been adequately studied. Certain abnormal subjects are more sensitive to salt, for example, diabetic children and certain patients with renal disease respond to increased salt intake with a rather prompt rise in blood pressure.

Nature of the Renal Defect

Subtle abnormalities in the ability of the kidney to excrete salt, perhaps genetic and age related, may determine individual susceptibility to a high salt intake.[1] Black subjects have a higher hypertensive morbidity and mortality, and seem prone to the low renin variety. Normotensive black subjects excrete a short-term intravenous sodium load over 24 hours less well than normotensive white subjects. Blood pressure increases with age. Normotensive subjects older than 40 years of age excrete a short-term intravenous sodium load slowly when compared with normotensive subjects younger than 40 years. Normotensive relatives of hypertensive subjects, especially the aged, also have a blunted natriuretic response.

This blunted response could result from renal functional or organic

changes.[1] For example, renal kallikrein, an enzyme that catalyzes the formation of kallidin, a natriuretic, diuretic and vasodilatory peptide, is found by some investigators excreted in lesser amounts by normotensive black subjects than by normotensive white subjects. Decreased generation of kallidin for a given state of sodium balance might contribute to the blunted natriuretic response to sodium among normotensive black subjects. Nephrosclerosis increases and glomerular filtration rate decreases with age in normotensive subjects. This, too, might contribute to the blunted natriuretic response. Regardless of the cause, blunted natriuresis for a given sodium load should result in increased sodium and water retention, and hence increased blood pressure in black and aged subjects relative to white and young subjects. Normotensive black subjects do, in fact, respond to a very large short-term increase in dietary salt intake with a greater blood pressure increase than normotensive white subjects. Furthermore, following the intravenous infusion of 2 liters of normal saline solution, blood pressure levels are significantly higher and plasma renin activity significantly lower in black subjects than white subjects. The higher prevalance of hypertension in the black population does not seem related to a greater dietary intake of sodium chloride, and several groups report an intake of sodium similar in black as compared to white subjects.

Other possibilities should also be considered. For example, a role for dopamine in the regulation of renal excretion of sodium is suggested by observations that dopamine has a natriuretic effect, its renal excretion parallels that of sodium, it has a tubular action and a dopamine antagonist attenuates the diuresis and natriuresis seen during infusion of Ringer's solution.[3] Thus, dopamine may be involved in the intrarenal regulation of sodium excretion, possibly acting as a local endogenous natriuretic factor. We need to determine whether this is in fact the case and, if so, whether this local mechanism is abnormal in those subjects prone to hypertension.

The influence of behavior should also be considered. It has been shown that the combination of avoidance conditioning and saline infusion can produce hypertension in dogs, whereas either one alone is without effect on blood pressure.[4] The combination can also reduce sodium excretion and urine flow.[5] These responses seem to result from increased sympathetic nervous system activity that reduces renal blood flow and glomerular filtration rate and increases tubular reabsorption of sodium and water[5] and renin secretion.[6] Similar responses have been observed in humans. Competitive mental tasks significantly reduce the urinary sodium and fluid excretion in young men with one or two hypertensive parents or with borderline hyper-

tension.[7] Thus, the blunted natriuresis in some cases may be mediated by psychological stress.

Evidence suggests that the Okamoto strain of spontaneously hypertensive rats, in addition to having abnormally permeable vascular smooth muscle cells with respect to sodium, also have kidneys which reabsorb sodium at an increased rate.[8,9] The cause of the latter is unknown, but could be increased permeability of the luminal membrane to sodium. Certain findings suggest that increased tubular reabsorption of sodium also occurs in the Milan strain of spontaneously hypertensive rats[10] and in hypertensive humans.[11]

Once essential hypertension is established, renal function is clearly abnormal (increased renal vascular resistance, decreased renal blood flow in many patients, increased filtration fraction, reduced urinary output at a given arterial pressure, exaggerated natriuresis, particularly in patients with low renin hypertension).[12] The abnormalities are no longer subtle, and it is easier to understand increased susceptibility to a high salt intake. This is underscored by the observation that, as in genetically hypertensive rats, essential hypertension in humans can be corrected by transplantation of a kidney from a normotensive donor which normalizes responses to salt deprivation and salt loading.[13]

POTASSIUM

Certain studies suggest that potassium may somehow be involved in the response to sodium.[1] For example, excess dietary sodium increases potassium excretion in normal man, and dietary potassium supplementation attenuates the blood pressure increase observed in these subjects receiving increased dietary sodium. The same is the case in diabetic children. Other studies suggest that potassium also lowers pressure in established hypertension, though this is controversial.[14] In theory, potassium administration should help rid the cells of sodium.The Na^+,K^+-ATPase and hence the Na^+-K^+ pump of vascular smooth muscle cells is sensitive to the extracellular concentration of potassium; an increase in extracellular potassium concentration stiumulates Na^+,K^+-ATPase and the pump.[15] Such stimulation causes vasodilation by hyperpolarizing the cell. Potassium can work in other ways.[1] Natriuresis can occur when potassium is administered, i.e., potassium may be antihypertensive in part by virtue of diuresis. Potassium may also cause vasodilation by stimulating Na^+,K^+-ATPase in the adrenergic nerve terminals and increasing the uptake of norepinephrine, thereby leaving less in the neuromuscular cleft. Potassium may also limit the increase in renin concentration caused by sodium restriction.

PREVENTION

Should the general public change its eating habits by reducing sodium intake? A number of investigators have advocated reduction in dietary intake of sodium chloride to prevent hypertension, and their view has received support from the Select Committee on GRAS Substances.[16] However, an equally large group of investigators do not support this view, and feel that such a recommendation for the general public is premature based on the available data. If we had some simple method to detect salt-sensitive individuals, we could concentrate on that group.

The daily requirement of man for sodium chloride is less than one gram, less than naturally occurs in most diets.[1] In the United States, the average adult daily intake is 10 to 12 grams, and much of this comes from processed foods. Adequate labeling of the sodium chloride content of foods clearly benefits those subjects known to be sensitive to salt, patients with renal disease, for example.

MECHANISMS

The link between salt intake and hypertension has received much attention, particularly during the last 10 years.[1,17-25] More than 30 years ago Tobian reported that the arteries of hypertensive subjects contain more sodium and water than the arteries of normotensive subjects. This was followed by debates as to the site of the extra sodium and water within the artery wall. Evidence was presented supporting both extracellular and intracellular deposition. There then followed a period during which attempts were made to determine the cause of presumed increased intracellular sodium. Increased permeability of vascular smooth muscle cells membrane to sodium and decreased activity of the sodium potassium pump in the sarcolemma of vascular smooth cells were considered, the latter resulting from a humoral sodium-potassium pump inhibitor (natriuretic hormone). It was suggested that the increased intracellular sodium caused increased intracellular calcium (by depolarizing the cell membrane or through a sodium-calcium exchange mechanism) and hence increased contractile activity and blood pressure.

At the present time, much activity is directed toward the role of natriuretic factors in linking salt intake to blood pressure.[23-25] We suggest that certain individuals have a genetic or acquired defect in the ability of the kidney to excrete salt. They encounter little difficulty while consuming small amounts of salt, but an increased salt intake results in sodium retention and hence increased blood volume. This is sensed by receptors in the lung which cause

the release of a small, heat and acid stable, nonpeptidic molecule (structure not yet determined) from the hypothalamus which has ouabain-like activity, i.e., it inhibits Na^+,K^+ATPase in the cardiovascular and renal systems and hence causes increased contractility in arteries, veins and heart, and natriuresis and diuresis. The latter is suboptimal because of the primary genetic or acquired renal defect. The effect of Na^+,K^+-ATPase inhibition on intracellular sodium concentration in the muscle of the cardiovascular system is more pronounced in those subjects who also have a genetic or acquired (e.g., mineralocorticoid) increase in cell membrane permeability to sodium.

More recently, another natriuretic factor has appeared upon the scene and is receiving even more attention.[26-29] This is the atrial natriuretic factor (ANF), packaged in specific granules within the cytoplasm of atrial myocytes. This factor, a peptide of known structure, produces prompt, massive, short-lived natriuresis and diuresis following intravenous injection. It may have a role in water and electrolyte homeostasis, being liberated from atrial myocytes by stretch when blood volume increases. Spontaneously hypertensive rats of the Okamoto strain have less extractable ANF in their atria, whereas Dahl salt-sensitive and reduced renal mass-saline hypertensive rats have more extractable ANF in their atria. Furthermore, the kidneys of Dahl salt-sensitive rats are less responsive to exogenous ANF. Thus, one might suggest that too little circulating ANF (due either to defective production or defective release) or kidneys which are relatively insensitive to it would promote hypertension through the mechanism described above. We shall need to assay blood levels of ANF to evaluate this suggestion. Raidoimmunoassays for ANF have been developed and should soon supply these data.

Summary

In this review we have summarized the evidence from animals and man for and against a role for dietary sodium in the genesis, treatment and prevention of hypertension. The evidence for a role in the genesis is strongest in those subjects with impaired excretory function. We then considered the nature of the renal defect which seems to make some individuals more susceptible to sodium intake. We next considered whether potassium intake can influence the relationship between sodium intake and blood pressure. Finally, we speculated upon the biochemical and biophysical links between sodium intake and hypertension, pointing out that the hypothalamic and atrial natriuretic factors are receiving much attention at the present time.

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